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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/829,968	04/11/2001	Klaus Peter Hirth	038602/1140	1137

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EXAMINER

HOLLERAN, ANNE L

ART UNIT PAPER NUMBER

1642

DATE MAILED: 05/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/829,968

Applicant(s)

HIRTH, KLAUS PETER

Examiner

Anne Holleran

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 27 February 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 20-25 and 27 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 20-25 and 27 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2/27/2004 has been entered.
2. Claims 20-25 and 27 are pending and examined on the merits.
3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections Withdrawn:

4. The rejection of claim 27 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention is withdrawn in view of the amendment.

Claim Rejections Maintained:

5. The rejection of claims 20-25 under 35 U.S.C. 103(a) as being unpatentable over Boocock (J. Nat. Cancer Inst., 87(7): 506-516, 1995) in view of Ferrara (WO 94/10202; published 11 May 1994) is maintained for the reasons of record.

Claims 20-23 are drawn to methods for detecting metastasis at a site distal from a primary tumor comprising administering to a human a detectably labeled ligand that specifically recognizes VEGF; and detecting the labeled ligand in the human, where abnormal presence of the labeled ligand indicates overexpression of VEGF at a site distal from the primary tumor and further indicates the presence of metastasis in the human. The ligand may be an anti-VEGF antibody, and VEGF receptor fusion protein or a VEGF receptor conjugated protein. The detection may be by a methods entailing X-ray, CAT-scan or MRI. Claims 24 and 25 are drawn to methods of claim 20 further comprising detecting co-expression of tyrosine kinase receptors involved in angiogenesis, where the receptors may be KDR/flk-1,flt-1 or tek/tie-2.

Boocock teaches that VEGF is detectable immunologically in sites of metastasis, and that VEGF expression is elevated compared to normal tissue (see page 511, 1st col.; and page 507, under Tissue collection and cell culture). Thus, Boocock teaches that VEGF is detectable in metastatic tissue. Boocock teaches that flt-1 is immunologically detectable in blood vessels that are adjacent to nests of tumor cells (page 513-514, bridging paragraph). Boocock also teaches that cell lines expressing VEGF RNA express VEGF receptor (flt and KDR) RNA (page 513, 1st col-2nd col., bridging paragraph).

Boocock fails to explicitly teach an *in vivo* method comprising the detection of VEGF.

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Ferrara teaches the use of VEGF antibodies and VEGF receptor proteins in *in vivo* methods of detection of VEGF and diagnosis (see page 12, lines 26-32; page 11, lines 31 - 37) and teaches that the methods of detection may be nuclear magnetic resonance (MRI is a detection method of nuclear magnetic resonance), or radiology (reads on CAT-scan and X-ray). Ferrara also teaches that angiogenesis plays an important role in tumor metastasis, and teaches that it is desirable to have a means of assaying for the presence of VEGF in pathological conditions such as cancer (page 2, lines 15-27).

Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have made a method for *in vivo* detection of VEGF for the detection of metastasis, and also to make a method that further comprises detection of angiogenic tyrosine kinase receptors, such as flt-1. One would have been motivated to make such a method because Ferrara teaches that it is desirable to have a means for assaying for the presence of VEGF in pathological conditions such as cancer, and because Boockock teaches that the VEGF is present in metastatic tumors. One would have had a reasonable expectation of success in making the claimed methods because of the teachings of Boockock that VEGF is present in metastatic tumors.

Applicant argues that the prior art fails to provide motivation to combine the teachings of Boockock with those of Ferrara. This is unpersuasive because the teachings of both Boockock and Ferrara are concerned with the role that VEGF plays in metastasis. Applicant attempts to argue that one of ordinary skill in the art would not be motivated by the teachings of Boockock to make a method for the *in vivo* detection of metastasis in an individual not yet known to have a metastatic tumor, because Boockock's teachings concern a patient that has already been diagnosed with metastasis. This argument is not persuasive because the teachings of Boockock are provided

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to demonstrate that the knowledge that VEGF expression was associated with metastasis was already in the prior art. Coupled with Ferrara teachings that detection of VEGF in vivo is useful for diagnosis, the claimed invention as a whole would have been obvious over the prior art.

New Grounds of Rejection:

6. Claims 20-25 and 27 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The basis for this rejection is that the amendment to claim 20 introduces new matter into the specification. Additionally, the specification fails to provide support for methods where metastasis is detected through a comparison of levels of VEGF ligand with levels of an individual not suffering from cancer, because the specification fails to describe “levels of labeled ligand” that is determined “from a person not suffering from cancer”.

The method of claim 20, as originally filed, was drawn to methods comprising the detection of “abnormal localization of VEGF”. Amending the claim to comprise steps where levels of VEGF in the human to be tested is compared to levels in a human not suffering from cancer changes the active steps of the claimed methods. A review of the specification shows that there does not appear to be support in the specification for methods comprising the general comparison of levels of VEGF ligand between a patient to be tested and an individual not suffering from cancer. Furthermore, it is noted that applicant fails to demonstrate where in the specification support for the claim amendments may be found.

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Additionally, the claims lack support from the specification because the specification fails to provide “levels” of VEGF bound to a labeled ligand that are exemplary of a “person not suffering from cancer”. Such levels are reference values that are not provided nor are methods for determining such reference levels contemplated in the specification. Therefore, the claimed inventions lack written description, and one of skill in the art would not find that applicant was in possession of the claimed inventions at the time the invention was filed.

7. Claims 20-23 are rejected under 35 U.S.C. 102(b) as being anticipated by Ferrara (WO 94/10202; published 11 May 1994).

Claims 20-23 are drawn to methods for detecting metastasis comprising administering to a human a detectably labeled ligand that specifically recognizes VEGF; and detecting the labeled ligand in the human, where detection of the labeled ligand indicates the presence of metastasis in the human. The ligand may be an anti-VEGF antibody, and VEGF receptor fusion protein or a VEGF receptor conjugated protein.

Ferrara teaches the use of VEGF antibodies and VEGF receptor proteins in *in vivo* methods of detection of VEGF and diagnosis (see page 12, lines 26-32; page 11, lines 31 - 37) and teaches that the methods of detection may be nuclear magnetic resonance (MRI is a detection method of nuclear magnetic resonance), or radiology (reads on CAT-scan and X-ray). Ferrara also teaches that angiogenesis plays an important role in tumor metastasis, and teaches that it is desirable to have a means of assaying for the presence of VEGF in pathological conditions such as cancer (page 2, lines 15-27). Thus, Ferrara teaches methods that are the same as that claimed.

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Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Office should be directed to Anne Holleran, Ph.D. whose telephone number is (571) 272-0833. Examiner Holleran can normally be reached Monday through Friday, 9:30 am to 2:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan, can be reached at (571) 272-0841.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist at telephone number (703) 571-1600.

Anne L. Holleran
Patent Examiner
May 17, 2004


GARY KUNZ
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